ACCESS DB # 144865

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SEARCH REQUEST FORM

Requester's Full Name: Kendra Carter Examiner #: 82283 Date: 7/7/96
Art Unit: 1617 Phone Number: 2-9034 Serial Number: 10/728261
Location (Bldg/Room#): Rem 4A10 (Mailbox #): 4B18 Results Format Preferred (circle): PAPER DISK

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Pharmaceutical composition of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine and uses thereof
Inventors (please provide full names): Herbert Harris; Robert Kucharik, Steven Leventer

Earliest Priority Date: 12/03/02

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

and its salt (see claim 1)

Please search the compound & its use in a composition and method.

thanks!!

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Type of Search

_____ NA Sequence (#)
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_____ STN _____ Dialog
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____ In-house sequence systems
____ Commercial ____ Oligomer ____ Score/Length
____ Interference ____ SPDI ____ Encode/Transl
_____ Other (specify)

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition according to claim 1, comprising (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine substantially free of the corresponding (*S*)-enantiomer; or a pharmaceutically acceptable salt thereof.

3. The composition according to claim 2 wherein the amount of (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or pharmaceutically acceptable salt thereof, in the composition is 85% by weight or more of the total weight of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine.

4. The composition according to claim 3 wherein the amount of (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or pharmaceutically acceptable salt thereof, in the composition is 90% by weight or more of the total weight of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine.

5. The composition according to claim 4 wherein the amount of (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or pharmaceutically acceptable salt thereof, in the composition is 95% by weight or more of the total weight of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine.

6. The composition according to claim 5 wherein the amount of (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine, or pharmaceutically acceptable salt thereof, in the composition

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L2           74 S KUCHARIK ?/AU
L3           53 S LEVENTER ?/AU
L4            3 S L1 AND L2 AND L3
                SEL L4 1-3 RN
                SEL L4 3 RN

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L6        81234 S ?BENZODIAZEPIN?/CNS
L7            3 S L5 AND L6

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L8            0 S L7

     FILE 'ZCAPLUS' ENTERED AT 12:06:05 ON 11 JUL 2006
L9           11 S L7



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L9 ANSWER 1 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:1242221 ZCAPLUS
DN 144:643
ED Entered STN: 25 Nov 2005
TI Benzodiazepine derivative phosphodiesterase inhibitors, and their therapeutic use
IN Bernard, Philippe Pierre
PA Greenpharma S.A., Fr.
SO Fr. Demande, 41 pp.
CODEN: FRXXBL
DT Patent
LA French
IC ICM C07D243-02
ICS A61K031-551; A61P025-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI FR 2870539	A1	20051125	FR 2004-5510	20040519
WO 2005113517	A1	20051201	WO 2005-FR1260	20050519

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI FR 2004-5510 A 20040519
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES

FR 2870539	ICM	C07D243-02
	ICS	A61K031-551; A61P025-00
	IPCI	C07D0243-02 [ICM,7]; C07D0243-00 [ICM,7,C*]; A61K0031-551 [ICS,7]; A61P0025-00 [ICS,7]
	ECLA	C07D243/02
WO 2005113517	IPCI	C07D0243-02 [ICM,7]; C07D0243-00 [ICM,7,C*]; A61K0031-551 [ICS,7]; A61P0025-00 [ICS,7]
	ECLA	C07D243/02

OS MARPAT 144:643

AB The invention discloses stereospecific derivs. of 2,3-benzodiazepines (Markush included) as inhibitors of phosphodiesterases, in particular phosphodiesterases 2 and 4, and their therapeutic use, particularly for the prevention and treatment of disease implying a central and/or peripheral disorder.

ST benzodiazepine deriv prepn phosphodiesterase inhibitor therapeutic

IT Brain, disease
Prion diseases
(Creutzfeldt-Jakob; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Inflammation
(Crohn's disease; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Intestine, disease
(Crohn's; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nervous system, disease
(Huntington's chorea; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Respiratory distress syndrome
(acute; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nervous system, disease
(amyotrophic lateral sclerosis; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Mental and behavioral disorders
(attention deficit disorder; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT AIDS (disease)
Aging, animal
Allergy
Allergy inhibitors
Alzheimer's disease

Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Antiarthritics
Anticonvulsants
Antidepressants
Antidiabetic agents
Antiobesity agents
Antiosteoporotic agents
Antiparkinsonian agents
Antipsychotics
Antirheumatic agents
Antitumor agents
Antiviral agents
Anxiety
Anxiolytics
Autoimmune disease
Central nervous system, disease
Cognition enhancers
Convulsion
Dermatitis
Diabetes mellitus
Down's syndrome
Drug delivery systems
Drug dependence
Epilepsy
Human
Human immunodeficiency virus
Infection
Inflammation
Memory disorders
Mental and behavioral disorders
Mononuclear cell (leukocyte)
Multiple sclerosis
Neoplasm
Nervous system agents
Neurogenesis
Obesity
Osteoarthritis
Osteoporosis
Parkinson's disease

Prion diseases
Prophylaxis
Psoriasis
Psychotropics
Rheumatoid arthritis
Schizophrenia
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Tumor necrosis factors
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Mental and behavioral disorders
(bipolar disorder; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Disease, animal
(central or peripheral; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nerve, disease
(chem.-caused; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Lung, disease
(chronic obstructive pulmonary disease; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nerve, disease
(degeneration; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Mental and behavioral disorders
(dementia; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Mental and behavioral disorders
(depression; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Mental and behavioral disorders
(diffuse Lewy body disease; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nervous system, disease
(dyskinesia; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Muscle, disease
(fibromyalgia; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems

(gels; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Inflammation
Kidney, disease
(glomerulonephritis; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems
(injections; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nerve, disease
(lesion; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Cytoprotective agents
(neuroprotective; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems
(oily; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Glaucoma (disease)
(optic nerve compression; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nerve, disease
(optic nerve injury, optic nerve compression; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Injury
(optic nerve, optic nerve compression; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems
(oral; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Nerve, disease
(peripheral neuropathy; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Eye, disease
Inflammation
(retinitis pigmentosa; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Eye, disease
(retinopathy; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Inflammation
Nose, disease

(rhinitis; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Shock (circulatory collapse)
(septic; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems
(solns., ophthalmic; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Brain, disease
(spongiform encephalopathy; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Brain, disease
(stroke; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Drug delivery systems
(tablets; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Spinal cord, disease
(trauma; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT Infection
(viral; benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT 60-92-4, Cyclic AMP 7665-99-8, Cyclic GMP 9025-82-5, Phosphodiesterase 9036-21-9, Phosphodiesterase IV 9040-59-9, Phosphodiesterase II
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT 22345-47-7P 869940-28-3P 869940-29-4P 869940-30-7P
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

IT 82059-50-5 82059-51-6 697754-50-0 **697754-53-3**
702693-86-5 792950-07-3 869940-02-3 869940-03-4
869940-04-5 869940-05-6 869940-06-7 869940-07-8 869940-08-9
869940-09-0 869940-10-3 869940-11-4 869940-12-5 869940-13-6
869940-14-7 869940-15-8 869940-16-9 869940-17-0 869940-18-1
869940-19-2 869940-20-5 869940-21-6 869940-22-7 869940-23-8
869940-24-9 869940-25-0 869940-26-1 869940-27-2
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

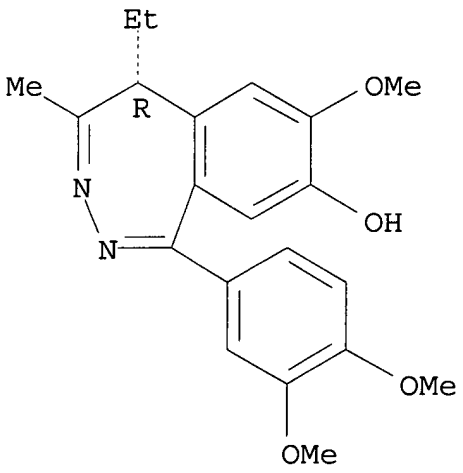
(1) Janus Pharmaceuticals Inc; WO 0024400 A 2000 ZCAPLUS
(2) Kucharik, R; WO 2004050080 A 2004 ZCAPLUS
(3) Kucharik, R; WO 2004073638 A 2004 ZCAPLUS
(4) Lagouge, Y; WO 02088096 A 2002 ZCAPLUS
(5) Schultz, D; WO 02098865 A 2002 ZCAPLUS

IT **697754-53-3 702693-86-5**
(benzodiazepine deriv. phosphodiesterase inhibitors, and therapeutic use)

RN 697754-53-3 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

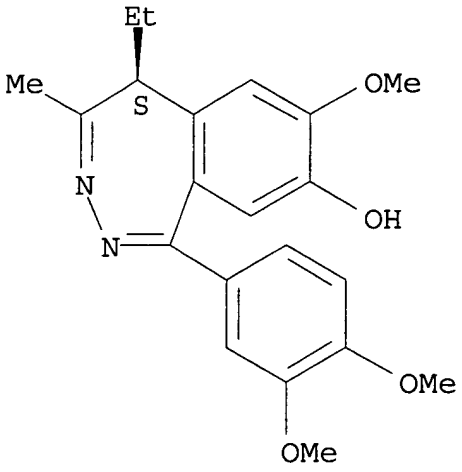
Absolute stereochemistry.



RN 702693-86-5 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 2 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:1080692 ZCAPLUS
DN 142:56375
ED Entered STN: 17 Dec 2004
TI Modulation of dopamine responses with substituted (S)-2,3-benzodiazepines
IN Leventer, Steven M.; Harris, Herbert W.; Kucharik, Robert F.
PA USA
SO U.S. Pat. Appl. Publ., 33 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-23 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004254173	A1	20041216	US 2003-461290	20030613
PRAI US 2003-461290		20030613		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES

US 2004254173	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513

OS MARPAT 142:56375

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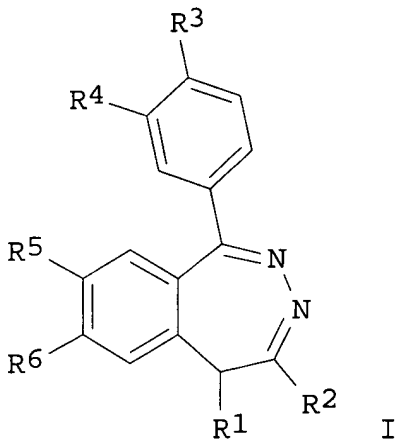


I

AB There is provided a method of modulating dopamine responses in the central nervous system of an individual or a method of treating a dopamine-mediated disorder in an individual not suffering from seizures or convulsions which comprises administering to the individual an effective amt. of at least one compd. of formula (I) [R1 = C1-7 hydrocarbyl or C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; wherein R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3, R4, R5, R6 = OH, C1-7 hydrocarbyl, CF3, C1-7 hydrocarbyloxy, acyloxy, NH2, -NH(C1-6alkyl), -N(C1-6 alkyl)2, -NH-acyl, halogen; wherein R5 and R6 may combine to form a 5-, 6- or 7-membered heterocyclic ring] or pharmaceutically acceptable salts thereof or said compd. comprising an (S)-enantiomer substantially free of the (R)-enantiomer of the same compd. The above dopamine-mediated disorder comprises a neurol. disorder or a

neuropsychiatric disorder. The neurol. disorder includes Huntington's chorea, Parkinson's disease, periodic limb movement syndrome, restless leg syndrome, hyperkinesias, Tourette's syndrome, Pick's disease, punch drunk syndrome, progressive subnuclear palsy, multiple systems atrophy, Landau-Kleffner syndrome, benign essential blepharospasm, amyotrophic lateral sclerosis, medication-induced movement disorders, and cognitive disorders. The neuropsychiatric disorder includes psychosis, personality disorders, psychiatric mood disorders, conduct and impulse disorders, schizophrenia, bipolar disorders, dysphoric mania, anxiety disorders, depression, panic disorders, agoraphobia, obsessive-compulsive disorders and eating disorders. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride was dissolved in methanol (35 mL) at a temp. of 40°. After cooling to 20-25°, hydrazine hydrate (0.75 g, 15 mmol, dissolved in 5 mL methanol) was added and the resulting mixt. was allowed to react while monitoring the reaction by HPLC and when complete, was evapd. to dryness. The residue was triturated with cold water (3 mL), filtered and dried to yield the crude 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic tofisopam) which was subsequently triturated with hot EtOAc to yield the pure product. Racemic tofisopam was resolved by a Chirobiotic V column (ASTEAC, Whippany, N.J.) to give (R)-tofisopam and (S)-tofisopam. (R)-tofisopam did not affect apomorphine-induced hypothermia in mice. Racemic tofisopam at 64 mg/kg tended to behave as a weak dopamine antagonist, i.e., lowering the rectal temp. at the thirty and sixty minute time points. However this trend was not statistically significant. (S)-tofisopam behaved as a weak dopamine antagonist at the 16 mg/kg dose at sixty minutes after apomorphine administration, i.e., showing a slight but statistically significant elevation in temp. At the higher doses, (S)-tofisopam demonstrated dopamine antagonism at both the thirty minute and sixty minute time points, i.e., lowering the rectal temp. at both time points.

ST benzodiazepine prepn modulation dopamine response; neurol disorder treatment benzodiazepine prepn; neuropsychiatric disorder treatment benzodiazepine prepn; tofisopam prepn modulation dopamine response

IT Brain, disease
(Gilles de la Tourette syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Nervous system, disease

(Huntington's chorea; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Disease, animal
(Landau-Kleffner syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(Pick's disease; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Stress, animal
(acute; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(agoraphobia; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Nervous system, disease
(amyotrophic lateral sclerosis; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Cachexia
(anorexia cachexia; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Appetite
(anorexia nervosa; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Disease, animal
(atrophy, multiple systems atrophy; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(bipolar disorder; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(dementia, hydrocephalic; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol.

disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(dementia, pseudo; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(dementia, subcortical; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(dementia; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(depression; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Nervous system, disease
(dystonia, acute dystonia; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Nervous system, disease
(extrapyramidal effects of neuroleptic agents; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Anxiety
(generalized; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(mania, dysphoric; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Movement disorders
(medication-induced; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Mental and behavioral disorders
(mood-affecting, psychiatric; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)
IT Nervous system, disease

(neuroleptic malignant syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(obsession-compulsion; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Anxiety
(panic disorder; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Leg
(periodic limb movement syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(personality disorder; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(post-traumatic stress disorder; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Antidepressants
Antiparkinsonian agents
Antipsychotics
Anxiety
Anxiolytics
Cognitive disorders
Eating disorders
Hyperkinesia
Learning disorders
Memory disorders
Mental and behavioral disorders
Mental and behavioral disorders
Nervous system, disease
Parkinson's disease
Schizophrenia
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Paralysis

(progressive subnuclear palsy; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Mental and behavioral disorders
(psychosis; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Disease, animal
(punch drunk syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Leg, disease
Sleep disorders
(restless leg syndrome; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Anxiety
(social; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT Muscle, disease
(spasm, benign essential blepharospasm; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 3943-77-9P, Ethyl 3,4-dimethoxybenzoate 6346-05-0P, 4-Methoxy-3-(phenylmethoxy)benzaldehyde 102728-10-9P, 3-(3,4-Dimethoxyphenyl)pentan-2-ol 185033-64-1P, Ethyl 3-methoxy-4-benzyloxybenzoate 618056-30-7P, 3-(3,4-Dimethoxyphenyl)pentan-3-ol 618056-32-9P, 4-((1Z)-1-Ethylprop-1-enyl)-1,2-dimethoxybenzene 618056-34-1P, 3-[4,5-Dimethoxy-2-[[4-methoxy-3-(phenylmethoxy)phenyl]carbonyl]phenyl]pentan-2-one 618056-36-3P, 3-[2-[(3-Hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 618056-40-9P, 4-(4-Ethyl-6,7-dimethoxy-3-methylisochromanyl)-1-methoxy-2-(phenylmethoxy)benzene 618056-41-0P, 4-((1Z)-1-Ethylprop-1-enyl)-1-benzyloxy-2-methoxybenzene 618056-42-1P, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochromanyl)-1,2-dimethoxybenzene 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-

methoxyphenyl]pentan-2-one
(intermediate; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT 51-61-6, Dopamine, biological studies
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT 74950-18-8P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 82059-50-5P, (R)-Tofisopam 82059-51-6P, (S)-Tofisopam 792950-07-3P, (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT 75114-20-4P, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

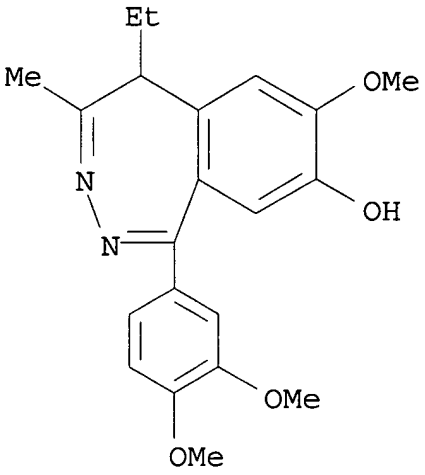
IT 22345-47-7P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **702693-86-5P**, (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 730962-81-9P, (S)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 792950-08-4P, (S)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT 64-17-5, Ethanol, reactions 75-03-6, Iodoethane 93-07-2, 3,4-Dimethoxybenzoic acid 100-39-0, Benzyl bromide 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6, 3-Methoxy-4-hydroxybenzoic acid 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 7803-57-8, Hydrazine hydrate 10467-10-4, Ethylmagnesium iodide 55300-10-2
(reactant; prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **702693-86-5P**,

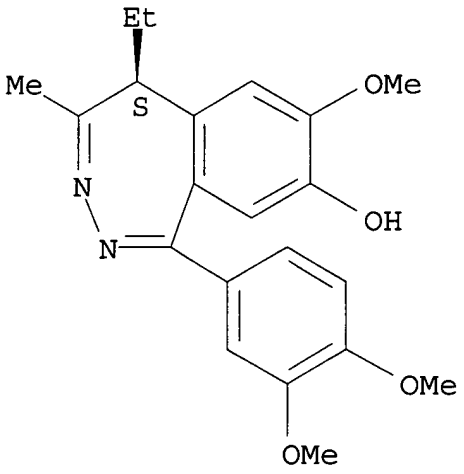
(S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

RN 95500-09-7 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



RN 702693-86-5 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 3 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:995773 ZCAPLUS
DN 141:410971
ED Entered STN: 19 Nov 2004
TI A preparation of 2,3-benzodiazepine derivatives, useful as antipyretic agents
IN Harris, Herbert W.; Kucharik, Robert F.
PA Vela Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 369,823.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004229866	A1	20041118	US 2004-781422	200402 17
	US 2004162284	A1	20040819	US 2003-369823	200302

	US 2004224943	A1	20041111	US 2004-827839	19 200404 19
PRAI	US 2003-369823	A2	20030219		
	US 2004-781422	A2	20040217		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004229866	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
US 2004162284	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
US 2004224943	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513

OS MARPAT 141:410971

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a prepn. of 2,3-benzodiazepine derivs. of formula I [wherein: R1 is hydrocarbyl or heteroalkyl; R2 is H or hydrocarbyl; R1 and R2 may combine to form a (carbo/hetero)cyclic ring; R3 and R4 are independently selected from OH, SH, NO2, halogen, or S-alkyl, etc.; R5 is substituted phenyl], useful as antipyretic agents. For instance, (S)-2,3-benzodiazepine deriv. II was prepd. via heterocyclization of diketone III with hydrazine and subsequent resoln. The prepd. title compds. were tested in stress-induced hypothermia assay. (S)-enantiomer of tofisopam showed higher activity than the racemate or the (R)-enantiomer [dose: 64 mg/kg, (S)-tofisopam: 33 °C, (R)-tofisopam: 35.25

°C, racemate: 33.75 °C].

ST tofisopam benzodiazepine prepn antipyretic; diketone hydrazine heterocyclization

IT Ischemia
(cerebral, treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Menopause
(disorder, hot flash, treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Brain, disease
(ischemia, treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Fever and Hyperthermia
(malignant, treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Antipyretics
Heterocyclization
(prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Brain, disease
(stroke, treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT Fever and Hyperthermia
Serotonin syndrome
(treatment of; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT 60142-96-3, Gabapentin
(drug component, GABA modulator; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT 105462-24-6, Risedronic acid 114084-78-5, Ibandronic acid
(drug component, bisphosphonate; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT 50-28-2, Estradiol, biological studies
(drug component, estrogen agonist; prepn. of benzodiazepine derivs. useful as antipyretic agents)

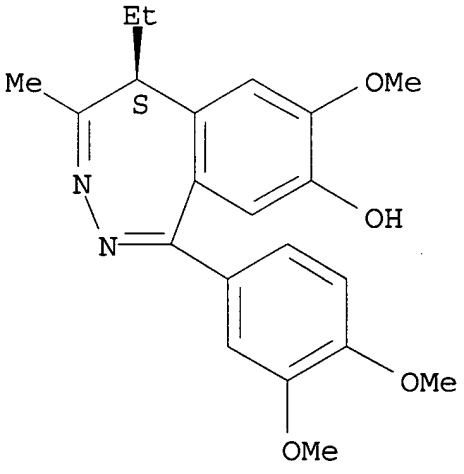
IT 84449-90-1, Raloxifen 198481-32-2, Bazedoxifene
(drug component, estrogen receptor agonist; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT 93413-69-5, Venlafaxine
(drug component, norepinephrine serotonin reuptake inhibitor; prepn. of benzodiazepine derivs. useful as antipyretic agents)

IT 74513-62-5, Trimegestone
(drug component, progesterone agonist; prepn. of benzodiazepine

derivs. useful as antipyretic agents)
IT 54910-89-3, Fluoxetine 61869-08-7, Paroxetine
(drug component, selective serotonin reuptake inhibitor; prepn. of benzodiazepine derivs. useful as antipyretic agents)
IT 82059-51-6P, (S)-Tofisopam **702693-86-5P**
(prepn. of benzodiazepine derivs. useful as antipyretic agents)
IT 730962-81-9P 792950-07-3P 792950-08-4P 792950-09-5P 792950-10-8P
(prepn. of benzodiazepine derivs. useful as antipyretic agents)
IT 75-03-6, Iodoethane 100-39-0, Benzyl bromide 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6 55300-10-2
(prepn. of benzodiazepine derivs. useful as antipyretic agents)
IT 617-05-0P 618056-37-4P 618056-38-5P 618056-39-6P 697754-57-7P
(prepn. of benzodiazepine derivs. useful as antipyretic agents)
IT **702693-86-5P**
(prepn. of benzodiazepine derivs. useful as antipyretic agents)
RN 702693-86-5 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 4 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:964818 ZCAPLUS
DN 141:410972
ED Entered STN: 12 Nov 2004

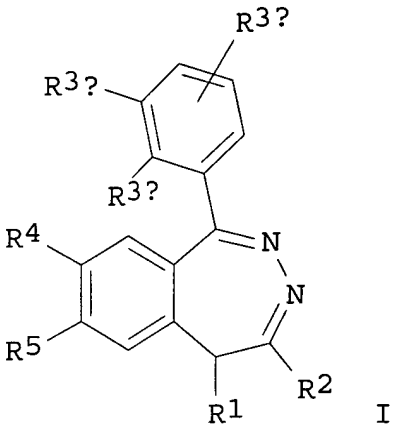
TI Preparation of (R)-2,3-benzodiazepine derivatives and method of lowering body temperature with them
IN Leventer, Steven M.; Kucharik, Robert F.
PA USA
SO U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 781,422.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004224943	A1	20041111	US 2004-827839	20040419
	US 2004162284	A1	20040819	US 2003-369823	20030219
	US 2004229866	A1	20041118	US 2004-781422	20040217
PRAI	US 2003-369823	A2	20030219		
	US 2004-781422	A2	20040217		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004224943	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
US 2004162284	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
US 2004229866	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]

IPCR A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
NCL 514/221.000
ECLA A61K031/5513
OS MARPAT 141:410972
GI



I

AB An (R)-2,3-benzodiazepine of formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3a, R3b, R3c = H, -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halogen; provided at least one of R3a, R3b and R3c is other than H; R4, R5 = -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halo; or R4 and R5 may combine to form a 5-, 6- or 7-membered heterocyclic ring], substantially free from the corresponding (S)-enantiomer thereof with respect to the abs. conformation at the 5-position of the benzodiazepine ring, is administered to lower the body temp. of an individual. More specifically, the administered compd. is (R)-tofisopam, or a pharmaceutically-acceptable salt thereof and said individual is afflicted with a disorder assocd. with an elevated body temp. such as fever, malignant hyperthermia, serotonin syndrome, or hot flashes during menopause or perimenopause or occurred as side effects of drug therapy or subsequent to the removal of estrogen-producing tissue. Furthermore said individual is afflicted with a disorder

such as cerebral ischemia or stroke wherein therapeutic benefit is achieved by lowering of the body temp. to a level below the normal body temp. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride was dissolved in methanol (35 mL) at 40°, cooled to 20-25°, treated with a soln. of hydrazine hydrate (0.75 g, 15 mmol)in 5 mL methanol, and allowed to reaction. The reaction was monitored by HPLC and when complete, was evapd. to dryness. The residue is triturated with cold water (3 mL), filtered, and dried to yield crude (RS)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic tofisopam). Racemic tofisopam was resolved by chiral chromatog. using a semipreparative Chirobiotic V column (ASTEC, Whippany, New Jersey) and Me tert-Bu ether/MeCN as the eluent to give (R)-tofisopam and (S)-tofisopam. In a stress induced hyperthermia assay using mice, racemic tofisopam demonstrated activity in lowering the core body temp. (S)-tofisopam was more active than either the racemate or the (R)-enantiomer. However, the (R)-enantiomer showed greater tolerability compared with either the racemate or the (S)-enantiomer. For example, the mice treated with the (R)-enantiomer showed less sedation, abnormal gait, or ptosis, decreased muscle tone, decreased lacrimation, or decreased reactivity to touch compared with either (S)-enantiomer or the racemate.

ST benzodiazepine tofisopam prepn lowering body temp; fever serotonin syndrome hot flash treatment benzodiazepine tofisopam prepn; malignant hyperthermia treatment benzodiazepine tofisopam prepn

IT Ischemia
(cerebral, therapeutic hypothermia in; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT Menopause
(disorder, hot flash; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT Brain, disease
(ischemia, therapeutic hypothermia in; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT Hypothermia
(malignant; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT Antipyretics
Body temperature
Combination chemotherapy
Fever and Hyperthermia
Hypothermia (therapeutic)
Serotonin syndrome
(prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT Brain, disease
(stroke, therapeutic hypothermia in; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT 50-28-2, Estradiol, biological studies 54910-89-3, Fluoxetine 60142-96-3, Gabapentin 61869-08-7, Paroxetine 74513-62-5, Trimegestone 84449-90-1, Raloxifene 93413-69-5, Venlafaxine 105462-24-6, Risedronic acid 114084-78-5, Ibandronic acid 198481-32-2, Bazedoxifene
(combination therapy agent; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 10467-10-4P, Ethylmagnesium iodide 55300-10-2P, 1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride 185033-64-1P, Ethyl 3-methoxy-4-benzyloxybenzoate 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 618056-41-0P, 4-[(1Z)-1-Ethylprop-1-enyl]-1-benzyloxy-2-methoxybenzene 618056-42-1P, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochroman-1-yl)-1,2-dimethoxybenzene 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-methoxyphenyl]pentan-2-one
(intermediate; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT 82059-50-5P, (R)-Tofisopam 82059-51-6P, (S)-Tofisopam
(prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT 74950-18-8P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine **95500-09-7P**,

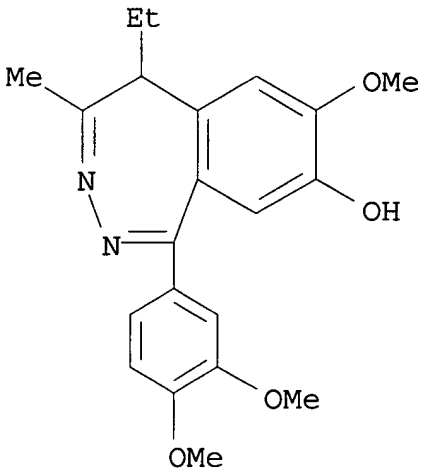
1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 697754-50-0P, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 697754-51-1P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 697754-52-2P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 697754-54-4P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 697754-55-5P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine **702693-86-5P**, (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT 64-17-5, Ethanol, reactions 75-03-6, Iodoethane 100-39-0, Benzyl bromide 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6, 3-Methoxy-4-hydroxybenzoic acid 7803-57-8, Hydrazine hydrate
(reactant; prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **702693-86-5P**, (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of (R)-2,3-benzodiazepine derivs. for lowering body temp. in fever, malignant hyperthermia, serotonin syndrome, or hot flashes)

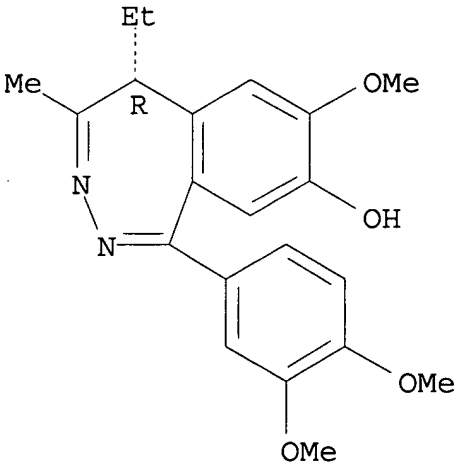
RN 95500-09-7 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



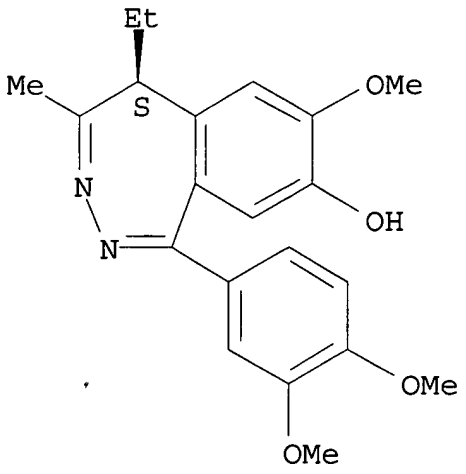
RN 697754-53-3 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 702693-86-5 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 5 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:570503 ZCAPLUS
DN 141:123662
ED Entered STN: 16 Jul 2004
TI A preparation of 2,3-benzodiazepine derivatives, useful for the treatment of inflammatory disorders
IN Kucharik, Robert F.; Harris, Herbert W.
PA Vela Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 32 pp., Cont.-in-part of U.S. Ser. No. 309,573.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004138209	A1	20040715	US 2003-727940	20031203
	US 2004106602	A1	20040603	US 2002-309573	20021203

03

US 6864251 B2 20050308

WO 2005056017 A1 20050623 WO 2004-US40403

200412
03

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-309573 A2 20021203

US 2003-727940 A 20031203

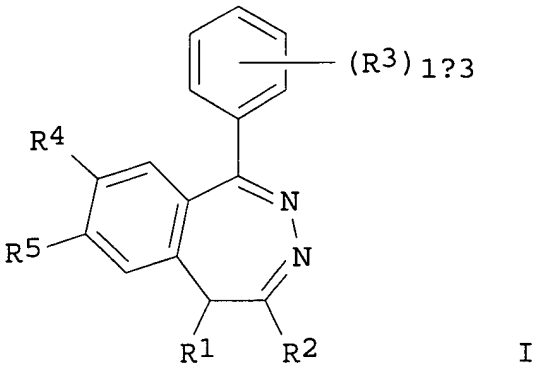
WO 2003-US38643 A 20031203

CLASS

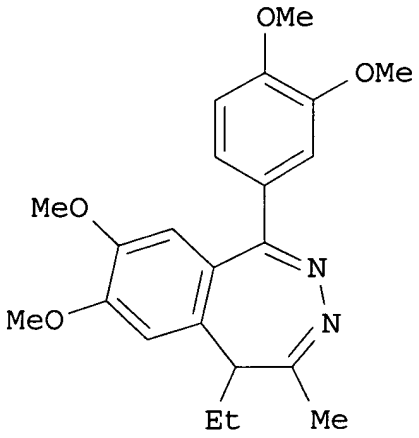
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004138209	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
US 2004106602	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513
WO 2005056017	IPCI	A61K0031-55 [ICM,7]
	IPCR	A61K0031-55 [I,A]; A61K0031-55 [I,C*]
	ECLA	A61K031/55

OS MARPAT 141:123662

GI



I



II

AB The invention relates to a prepn. of 5H-2,3-benzodiazepine derivs. of formula I [wherein: R1 is (hetero)alkyl; R2 is H or alkyl; R3 is alkoxy, OH, SH, or NH2, etc.; R4 and R5 are independently selected from alkoxy, OH, NH2, NH-acyl, or halogens, etc.], useful for the treatment of inflammatory disorders, particularly inflammatory disorders mediated by LTB4. For instance, prepd. (R)-5-ethyl-2,3-benzodiazepine deriv. II was screened in LTB4 binding assay (Ki = 0.444 μM, table 2).

ST benzodiazepine prepn inflammatory disorder LTB4 binding

IT Digestive tract, disease
Inflammation
(gastroenteritis, radiation-induced, treatment of; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT Intestine, disease
(inflammatory, treatment of; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT Leukotriene receptors
(leukotriene B4, treatment of disease mediated by; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT Heterocyclic compounds
(nitrogen; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT Anti-inflammatory agents
Antirheumatic agents
Human
Inflammation

(prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT Psoriasis
Rheumatoid arthritis
(treatment of; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 446-86-6, Azathioprine
(drug component, antimetabolic; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 53-03-2, Prednisone 51333-22-3, Budesonide
(drug component, corticosteroid; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 59865-13-3, Cyclosporine 104987-11-3, Tacrolimus
(drug component, immunosuppressant; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 119477-85-9, U-75302 120072-59-5, SC41930 134578-96-4, ONO-4057 147398-01-4, CGS-25019C 153633-01-3, SC53228 158081-99-3, CP-105696 161172-51-6, VML295 204981-48-6, CP-195543
(drug component, leukotriene antagonist; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 54845-95-3, 15-HETE 75706-12-6, Leflunomide
(drug component, leukotriene inhibitor; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 170277-31-3, Infliximab 185243-69-0, Etanercept 331731-18-1, Adalimumab
(drug component, tumor necrosis factor alpha inhibitor; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 89-57-6, Mesalamine 599-79-1, Sulfasalazine
(drug component; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 617-05-0P 6346-05-0P 102728-10-9P 185033-64-1P 618056-30-7P 618056-32-9P 618056-34-1P 618056-36-3P 618056-37-4P 618056-38-5P 618056-39-6P 618056-40-9P 618056-41-0P 618056-42-1P 697754-57-7P
(intermediate; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 74950-18-8P
(prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 264-22-2DP, 5H-2,3-Benzodiazepine, derivs. 22345-47-7P 74950-24-6P 74950-36-0P 75114-20-4P 82059-50-5P 82059-51-6P

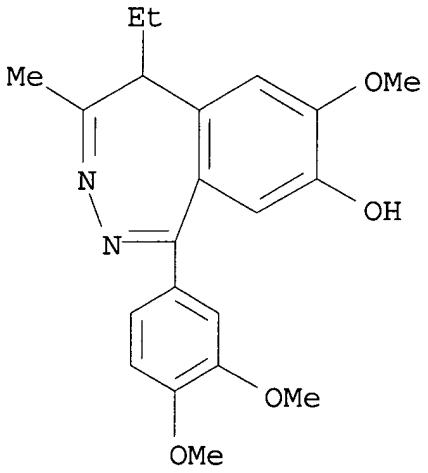
95500-09-7P 697754-50-0P 697754-51-1P 697754-52-2P
697754-53-3P 697754-54-4P 697754-55-5P
(prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT 93-07-2, 3,4-Dimethoxybenzoic acid 121-33-5 121-34-6 621-59-0 722456-98-6
(reactant; prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

IT **95500-09-7P 697754-53-3P**
(prepn. of benzodiazepine derivs. useful for the treatment of inflammatory disorders)

RN 95500-09-7 ZCAPLUS

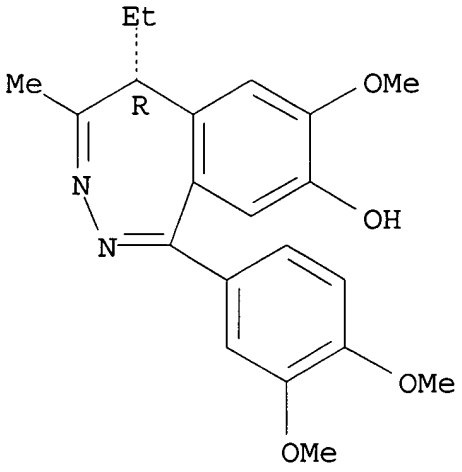
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



RN 697754-53-3 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



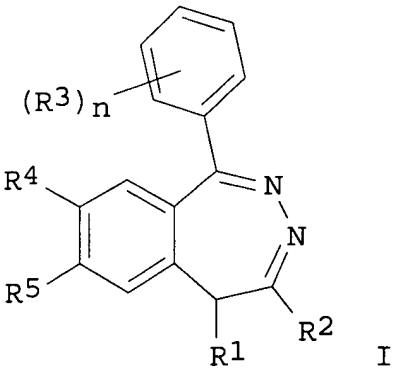
L9 ANSWER 6 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:569860 ZCAPLUS
DN 141:123661
ED Entered STN: 16 Jul 2004
TI Method of increasing neutrophil production using 2,3-benzodiazepines
IN Harris, Herbert W.; Kucharik, Robert F.
PA Vela Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 29 pp., Cont.-in-part of U.S. Ser. No. 309,527.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004138210	A1	20040715	US 2003-728286	20031202
	US 2004106601	A1	20040603	US 2002-309527	20021203

US 7022700 B2 20060404
PRAI US 2002-309527 A2 20021203
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004138210	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513; A61K031/5513+M; A61K045/06
US 2004106601	IPCI	A61K0031-55 [I,A]; A61K0031-553 [I,A]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513; A61K031/5513+M; A61K045/06

OS MARPAT 141:123661
GI



I

AB Claimed is a method of increasing the abs. neutrophil count in an individual, comprising administering to said individual an effective amt. of at least one compd. according to formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; wherein R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3 is independently selected from the group consisting of C1-6 alkoxy, OH, acyloxy, SH, C1-3 alkylthio, NH2, C1-6 alkylamino, di(C1-6 alkyl)amino, acylamino, NO2 and halogen; n

= 1, 2 or 3; R4 and R5 are independently selected from the group consisting of C1-6 alkoxy, OH, acyloxy, SH, C1-3 alkylthio, NH2, acylamino, and halogen; wherein, R4 and R5 may combine to form a 5, 6 or 7-membered heterocyclic ring] or pharmaceutically-acceptable salts thereof. Also claimed is a method of treating an individual afflicted with neutropenia or preventing neutropenia in an individual who is at risk of developing neutropenia, comprising administering to said individual an effective amt. of at least one compd. I. The neutropenia treated is a side effect of exposure of an individual to ionizing radiation, in particular in therapeutic radiation therapy or the neutropenia developed is assocd. with immunodeficiency, in particular cancer or virus such as immunodeficiency virus. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride was dissolved in 35 mL MeOH at 40°, cooled to 20-25°, treated with a soln. of hydrazine hydrate (0.75 g, 15 mmol) in 5 mL MeOH, allowed to react while monitoring by HPLC and when complete, evapd. to dryness, triturated with cold water (3 mL), filtered, dried to yield the crude 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine which was subsequently triturated with hot EtOAc to give the pure product. (R)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzo diazepine [(R)-tofisopam] significantly increased the neutrophil levels in a dose-dependently manner, e.g. by 29, 47, and 63% at 100, 200, 400 mg/kg/day, resp., for 15 days in female CD(SD)IGS BR rats.

ST benzodiazepine prepn neutrophil prodn increase; neutropenia treatment prevention side effect ionizing radiation; therapeutic radiation therapy side effect neutropenia treatment benzodiazepine prepn

IT Glycosides
(amino, combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Sulfonamides
(antibiotics, combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Chelating agents
Rauvolfia

(combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Tetracyclines
(combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Immunodeficiency
(neutropenia assocd. with immunodeficiency; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Agranulocytosis
(neutropenia; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT Ionizing radiation
Neutrophil
Radiotherapy
(prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 83-12-5, 2-Phenyl1,3-indanedione
((phenindone), combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-49-7, Imipramine 50-78-2, Aspirin 51-06-9, Procainamide 51-28-5, Dinitrophenol, biological studies 51-52-5, Propylthiouracil 52-01-7, Spironolactone 52-67-5, Penicillamine 52-86-8, Haloperidol 53-86-1, Indomethacin 54-05-7, Chloroquine 54-85-3, Isoniazid 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-53-4, Meprobamate 58-14-0, Pyrimethamine 58-15-1, Aminopyrine 58-54-8, Ethacrynic acid 58-94-6D, Thiazide, derivs. 59-66-5, Acetazolamide 59-92-7, Levodopa, biological studies 60-56-0, Methimazole 64-77-7, Tolbutamide 64-86-8, Colchicine 67-20-9, Nitrofurantoin 67-52-7D, 2,4,6(1H,3H,5H)-Pyrimidinetrione, derivs. 68-89-3, Dipyrone 74-55-5, Ethambutol 80-08-0, Dapsone

83-89-6, Quinacrine 86-22-6, Brompheniramine 86-54-4, Hydralazine 89-57-6, Mesalazine 91-81-6, Tripelennamine 92-84-2D, Phenothiazine, derivs. 94-20-2, Chloropropamide 99-66-1, Valproic acid 104-06-3, Thiacetazone 118-42-3, Hydroxychloroquine 123-56-8D, Succinimide, derivs. 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-48-0, Trimethadione 130-95-0, Quinine 141-90-2, Thiouracil 298-46-4, Carbamazepine 302-04-5, Thiocyanate, biological studies 302-79-4, Retinoic acid 303-49-1, Clomipramine 315-30-0, Allopurinol 364-62-5, Metoclopramide 364-98-7, Diazoxide 461-72-3D, Hydantoin, derivs. 493-78-7, Methaphenilene 525-66-6, Propranolol 554-57-4, Methazolamide 555-30-6, Methyldopa 599-79-1, Sulfasalazine 738-70-5, Trimethoprim 1404-55-3, Ristocetin 1406-05-9, Penicillin 2022-85-7, Flucytosine 2784-55-6, Thenalidine 3313-26-6, Thiothixene 5786-21-0, Clozapine 7778-74-7, Potassium perchlorate 10540-29-1, Tamoxifen 11111-12-9D, Cephalosporin, derivs. 12794-10-4D, Benzodiazepine, derivs. 13292-46-1, Rifampin 13311-84-7, Flutamide 14028-44-5, Amoxapine 14769-73-4, Levamisole 15687-27-1, Ibuprofen 21679-14-1, Fludarabine 22232-54-8, Carbimazole 22494-42-4, Diflunisal 24219-97-4, Mianserin 26171-23-3, Tolmetin 27790-75-6D, Dihydropyridine, derivs. 30516-87-1, Zidovudine 31431-39-7, Mebendazole 36877-68-6, Nitroimidazole 37640-71-4, Aprindine 38194-50-2, Sulindac 41859-67-0, Bezafibrate 51234-28-7, Benoxaprofen 51481-61-9, Cimetidine 54063-53-5, Propafenone 55142-85-3, Ticlopidine 59277-89-3, Acyclovir 62571-86-2, Captopril 64221-86-9, Imipenem 66357-35-5, Ranitidine 76824-35-6, Famotidine 81627-83-0, Macrophage colony stimulating factor 81840-15-5, Vesnarinone 82009-34-5, Cilastatin 83869-56-1, Granulocyte macrophage colony stimulating factor 85721-33-1, Ciprofloxacin 91161-71-6, Terbinafine 106266-06-2, Risperidone 143011-72-7, Granulocyte colony stimulating factor (combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 3943-77-9P, Ethyl 3,4-dimethoxybenzoate 6346-05-0P, 4-Methoxy-3-(phenylmethoxy)benzaldehyde 10467-10-4P, Ethylmagnesium Iodide 102728-10-9P, 3-(3,4-Dimethoxyphenyl)pentan-2-ol 185033-64-1P, Ethyl 3-methoxy-4-benzyloxybenzoate 618056-30-7P, 3-(3,4-Dimethoxyphenyl)pentan-3-ol 618056-32-9P,

4-((1Z)-1-Ethylprop-1-enyl)-1,2-dimethoxybenzene 618056-34-1P, 3-[4,5-Dimethoxy-2-[[4-methoxy-3-(phenylmethoxy)phenyl]carbonyl]phenyl]pentan-2-one 618056-36-3P, 3-[2-[(3-Hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 618056-40-9P, 4-(4-Ethyl-6,7-dimethoxy-3-methylisochromanyl)-1-methoxy-2-(phenylmethoxy)benzene 618056-41-0P, 4-((1Z)-1-Ethylprop-1-enyl)-1-benzyloxy-2-methoxybenzene 618056-42-1P, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochromanyl)-1,2-dimethoxybenzene 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-methoxyphenyl]pentan-2-one
(intermediate; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 697754-50-0P, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 22345-47-7P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 74950-18-8P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 74950-21-3P, 1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 74950-24-6P, 1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 74950-36-0P, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 75114-20-4P, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 82059-50-5P, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 697754-51-1P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 697754-52-2P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 697754-54-4P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine

697754-55-5P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

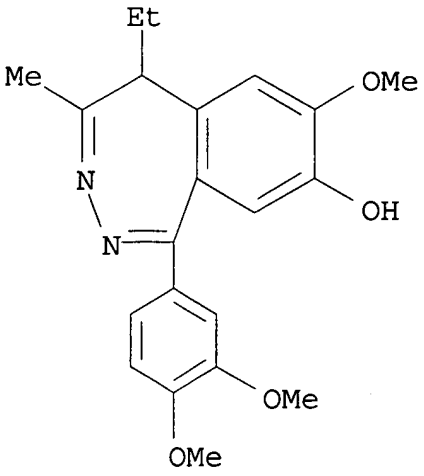
IT 64-17-5, Ethanol, reactions
(reactant, combination therapy; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT 75-03-6, Iodoethane 93-07-2, 3,4-Dimethoxybenzoic Acid 100-39-0, Benzyl bromide 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6, 3-Methoxy-4-hydroxybenzoic Acid 302-01-2, Hydrazine, reactions 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 55300-10-2, 1-(3,4-Dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride
(reactant; prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for increasing neutrophil prodn. to prevent or treat neutropenia developed as side effect of exposure to ionizing radiation in therapeutic radiation therapy.)

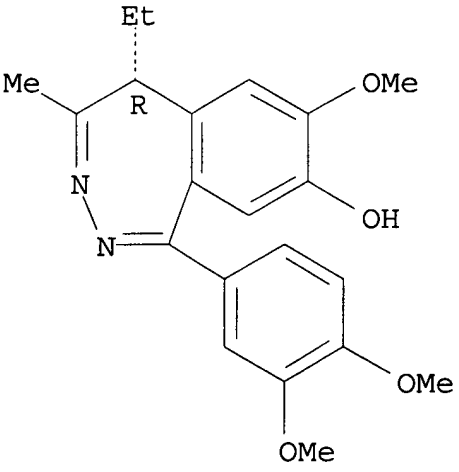
RN 95500-09-7 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



RN 697754-53-3 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 7 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:490707 ZCAPLUS
DN 141:33842
ED Entered STN: 17 Jun 2004
TI Pharmaceutical composition of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine and uses thereof

IN Kucharik, Robert F.; Leventer, Steven M.; Harris, Herbrt W.
PA Vela Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-12 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004050040	A2	20040617	WO 2003-US38642	20031203
	WO 2004050040	A3	20050331		
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	AU 2003293405	A1	20040623	AU 2003-293405	20031203
	US 2004157833	A1	20040812	US 2003-728261	20031203
	EP 1567161	A2	20050831	EP 2003-790352	20031203
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PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2006510634 T2 20060330 JP 2004-557606 200312 03

PRAI US 2002-430771P P 20021203

WO 2003-US38642 W 20031203

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004050040	ICM	A61K
	IPCI	A61K [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551
CA 2508542	IPCI	A61K0031-55 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551
AU 2003293405	IPCI	A61K0031-55 [ICM,7]
US 2004157833	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	NCL	514/221.000
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EP 1567161	IPCI	A61K0031-55 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551
JP 2006510634	IPCI	A61K0031-551 [I,A]; C07D0491-056 [I,A]; C07D0491-00 [I,C*]; A61P0029-00 [I,A]; A61P0001-00 [I,A]; A61P0001-04 [I,A]; A61P0017-06 [I,A]; A61P0017-00 [I,C*]; A61P0019-02 [I,A]; A61P0021-00 [I,A]; A61P0025-04 [I,A]; A61P0015-00 [I,A]; A61P0019-00 [I,A]; A61P0025-00 [I,A]; A61P0025-24 [I,A]; A61P0025-28 [I,A]; A61P0025-16 [I,A]; A61P0037-02 [I,A]; A61P0037-00 [I,C*]; A61P0011-06 [I,A]; A61P0011-00 [I,C*]; A61P0035-00 [I,A]; A61P0009-00 [I,A]; A61P0025-08 [I,A]; A61P0025-06 [I,A]; A61P0009-04 [I,A]; A61P0009-12 [I,A]; A61P0013-12 [I,A]; A61P0013-00 [I,C*]; A61P0027-06 [I,A]; A61P0027-00 [I,C*]
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4C086/ZA01; 4C086/ZA06; 4C086/ZA08; 4C086/ZA12; 4C086/ZA15; 4C086/ZA18; 4C086/ZA22; 4C086/ZA33; 4C086/ZA36; 4C086/ZA39; 4C086/ZA42; 4C086/ZA59; 4C086/ZA66; 4C086/ZA68; 4C086/ZA81; 4C086/ZA89; 4C086/ZA94; 4C086/ZA96; 4C086/ZB07; 4C086/ZB11; 4C086/ZB15; 4C086/ZB26; 4C086/ZC71

AB Pharmaceutical compns. comprising 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine (I) or a pharmaceutically acceptable salt thereof are described. The compns. are used for treating, preventing or delaying the onset of disorders mediated by LTB4, TXA2 or adenosine. For example, I demonstrated statistically significant anticonvulsant activity at 30 and 45 mg/kg doses. The 60 mg dose showed comparable anticonvulsant activity, but fell short of statistical significance. This is likely a consequence of the small no. of tested animals,.

ST benzodiazepine deriv prepn inflammation central nervous system disease; adenosine disease mediation benzodiazepine deriv; leukotriene B4 disease mediation benzodiazepine deriv; thromboxane A2 disease mediation benzodiazepine deriv

IT Inflammation
(Crohn's disease; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Intestine, disease
(Crohn's; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Myelosuppression
(assocd. with cytotoxic chemotherapy or radiotherapy; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Angiogenesis
(assocd. with developing tumor; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Mental and behavioral disorders
(attention deficit disorder; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Mental and behavioral disorders
(autism; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Ischemia
(cerebral; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Fatigue, biological

(chronic fatigue syndrome; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Inflammation
(chronic; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Artery, disease
(coronary; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Nerve, disease
(death; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Mental and behavioral disorders
(depression; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Jaw
(disease, osteonecrosis; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Heart, disease
Kidney, disease
(failure; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Muscle, disease
(fibromyalgia; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Digestive tract, disease
Inflammation
(gastroenteritis, radiation-induced; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Intestine, disease
(inflammatory; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Adenosine receptors
Thromboxane receptors
(inhibition of ligand binding to; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Brain, disease
(ischemia, transient; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Brain, disease
(ischemia; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT Lyme disease
(late lyme disease; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Leukotriene receptors
(leukotriene B4, inhibition of ligand binding to; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Headache
(migraine; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Cell death
(neuron; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Anti-inflammatory agents
Asthma
Epilepsy
Fertility disorders
Glaucoma (disease)
Hypertension
Inflammation
Multiple sclerosis
Nervous system agents
Pain
Parkinson's disease
Psoriasis
Rheumatoid arthritis
Sjogren syndrome
Wound healing promoters
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Brain, disease
(stroke; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Ischemia
(transient cerebral; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT Inflammation
Intestine, disease
(ulcerative colitis; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)
IT 58-61-7, Adenosine, biological studies
(central nervous system disorders mediated by; prepn. of

benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT 57576-52-0, Thromboxane A2
(disorders mediated by; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT 71160-24-2, LTB4
(inflammation mediated by; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-methoxyphenyl]pentan-2-one
(prepn. and debenzylation of; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT 618056-42-1P, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochromanyl)-1,2-dimethoxybenzene
(prepn. and ring opening of; prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **702693-86-5P**
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6, 3-Methoxy-4-hydroxybenzoic acid
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

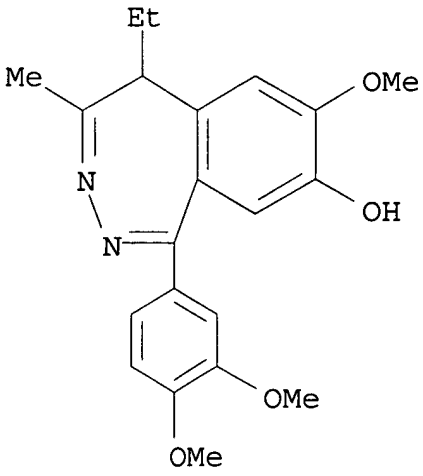
IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 618056-41-0P, 4-((1Z)-1-Ethylprop-1-enyl)-1-benzyloxy-2-methoxybenzene
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

RN 95500-09-7 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-

4-methyl- (9CI) (CA INDEX NAME)

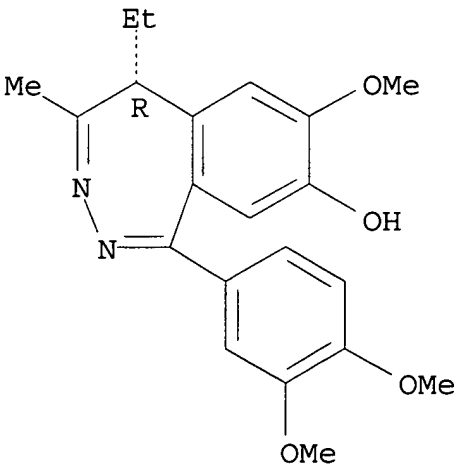


IT **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine **702693-86-5P**
(prepn. of benzodiazepine deriv. for treatment of disorders mediated by adenosine, LTB4 or TXA2)

RN 697754-53-3 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

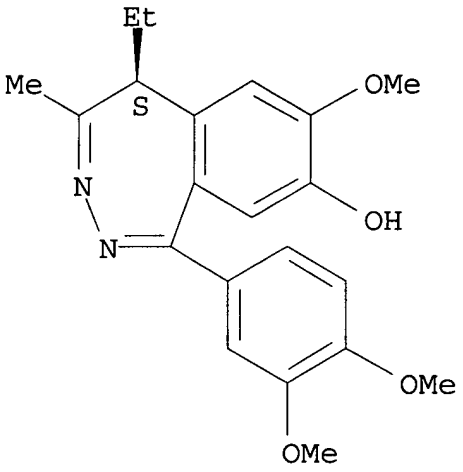
Absolute stereochemistry.



RN 702693-86-5 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 8 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:451631 ZCAPLUS
DN 141:23558
ED Entered STN: 04 Jun 2004
TI Preparation of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders
IN Kucharik, Robert F.; Harris, Herbert W.
PA Vela Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004106602	A1	20040603	US 2002-309573	200212

03

US 6864251 B2 20050308

CA 2508312 AA 20040617 CA 2003-2508312

200312
03

WO 2004050080 A1 20040617 WO 2003-US38643

200312
03

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AU 2003298913 A1 20040623 AU 2003-298913

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US 2004138209 A1 20040715 US 2003-727940

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EP 1581206 A1 20051005 EP 2003-796673

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JP 2006510635 T2 20060330 JP 2004-557607

200312
03

PRAI US 2002-309573 A 20021203

WO 2003-US38643 W 20031203

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004106602	ICM	A61K031-5513
	INCL	514221000

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	ECLA	A61K031/5513
CA 2508312	IPCI	A61K0031-33 [ICM,7]; A61K0031-55 [ICS,7]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
	ECLA	A61K031/5513
WO 2004050080	IPCI	A61K0031-33 [ICM,7]; A61K0031-55 [ICS,7]
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AU 2003298913	IPCI	A61K0031-33 [ICM,7]; A61K0031-55 [ICS,7]
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EP 1581206	IPCI	A61K0031-33 [ICM,7]; A61K0031-55 [ICS,7]
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JP 2006510635	IPCI	A61K0031-551 [I,A]; C07D0243-02 [I,A]; C07D0243-00 [I,C*]; A61K0045-00 [I,A]; A61P0029-00 [I,A]; A61K0031-635 [I,A]; A61K0031-63 [I,C*]; A61K0031-606 [I,A]; A61K0031-60 [I,C*]; A61K0031-573 [I,A]; A61K0031-57 [I,C*]; A61K0031-58 [I,A]; A61K0031-52 [I,A]; A61K0031-519 [I,C*]; A61K0038-00 [I,A]; A61K0031-436 [I,A]; A61K0031-4353 [I,C*]; A61K0039-395 [I,A]; A61K0031-222 [I,A]; A61K0031-21 [I,C*]; A61K0031-42 [I,A]; A61K0031-557 [I,A]; A61P0001-04 [I,A]; A61P0017-06 [I,A]; A61P0019-02 [I,A]; A61P0019-06 [I,A]; A61P0019-00 [I,C*]; A61P0001-02 [I,A]; A61P0001-00 [I,C*]; A61P0011-02 [I,A]; A61P0011-00 [I,C*]; A61P0037-08 [I,A]; A61P0037-00 [I,C*]; A61P0017-00 [I,A]; A61P0027-02 [I,A]; A61P0027-00 [I,C*]
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4C084/ZA892; 4C084/ZA962; 4C084/ZB112;
4C084/ZB132; 4C084/ZB152; 4C084/ZC312;
4C085/AA14; 4C085/BB31; 4C085/CC23; 4C085/EE03;
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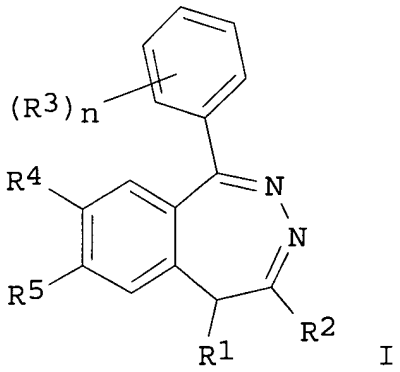
OS MARPAT 141:23558

GI



I

AB Disclosed is a method of treating an individual afflicted with an inflammatory disorder mediated by leukotriene B4 (LTB4) comprising administering to said individual an effective amt. of at least one compd. according to formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3 = C1-6 alkoxy, OH, acyloxy, SH, C1-3 alkylthio, NH2, mono or di(C1-6 alkyl)amino, acylamino, NO2, halo; n = 1, 2, 3; R4, R5 = C1-6

alkoxy, OH, acyloxy, SH, C1-3 alkylthio, NH2, acylamino, halo; or R4 and R5 may combine to form a 5, 6 or 7-membered heterocyclic ring; wherein, the compds. according to this formula are (R)-enantiomers substantially free of the corresponding (S)-enantiomers, with respect to the abs. conformation at the 5-position of the benzodiazepine ring] or pharmaceutically acceptable salts thereof. Inflammatory disorders mediated by LTB4 include inflammatory bowel disease, ulcerative colitis, psoriasis, rheumatoid arthritis, Crohn's disease and radiation-induced gastrointestinal inflammation. Thus, 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride was cyclocondensed with hydrazine hydrate at 20-25° in MeOH gave (R,S)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine [(R,S)-II] which was resolved by a Chirobiotic V column (ASTEAC, whippany, N.J.) to give (R)-II. (R,S)-, (R)-, and (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (tofisopam) showed the binding affinity to LTB4 receptor with Ki of 4.52, 0.444, and 76.0 μM, resp.

ST benzodiazepine prepn treatment LTB4 mediated inflammatory disorder

IT Inflammation
(Crohn's disease; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT Intestine, disease
(Crohn's; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT Digestive tract, disease
Inflammation
(gastroenteritis, radiation-induced; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT Intestine, disease
(inflammatory; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT Anti-inflammatory agents
Antirheumatic agents
Inflammation
Psoriasis
Rheumatoid arthritis
(prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT Inflammation

Intestine, disease
(ulcerative colitis; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 3943-77-9P, Ethyl 3,4-dimethoxybenzoate 6346-05-0P, 4-Methoxy-3-(phenylmethoxy)benzaldehyde 10467-10-4P, Ethylmagnesium iodide 102728-10-9P, 3-(3,4-Dimethoxyphenyl)pentan-2-ol 185033-64-1P, Ethyl 3-methoxy-4-benzyloxybenzoate 618056-30-7P, 3-(3,4-Dimethoxyphenyl)pentan-3-ol 618056-32-9P, 4-((1Z)-1-Ethylprop-1-enyl)-1,2-dimethoxybenzene 618056-34-1P, 3-[4,5-Dimethoxy-2-[[4-methoxy-3-(phenylmethoxy)phenyl]carbonyl]phenyl]pentan-2-one 618056-36-3P, 3-[2-[(3-Hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 618056-40-9P, 4-(4-Ethyl-6,7-dimethoxy-3-methylisochromanyl)-1-methoxy-2-(phenylmethoxy)benzene 618056-41-0P, 4-((1Z)-1-Ethylprop-1-enyl)-1-benzyloxy-2-methoxybenzene 618056-42-1P, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochromanyl)-1,2-dimethoxybenzene 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-methoxyphenyl]pentan-2-one
(intermediate; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT 82059-51-6P, (S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
(prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT 82059-50-5P, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 697754-50-0P, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT 22345-47-7P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 74950-18-8P, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 75114-20-4P, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-

benzodiazepine 697754-51-1P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 697754-52-2P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine 697754-54-4P, (R)-1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 697754-55-5P, (R)-1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

IT 64-17-5, Ethanol, reactions 75-03-6, Iodoethane 93-07-2, 3,4-Dimethoxybenzoic acid 100-39-0, Benzyl bromide 120-14-9, 3,4-Dimethoxybenzaldehyde 121-34-6, 3-Methoxy-4-hydroxybenzoic acid 302-01-2, Hydrazine, reactions 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 7803-57-8, Hydrazine hydrate 55300-10-2
(reactant; prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD

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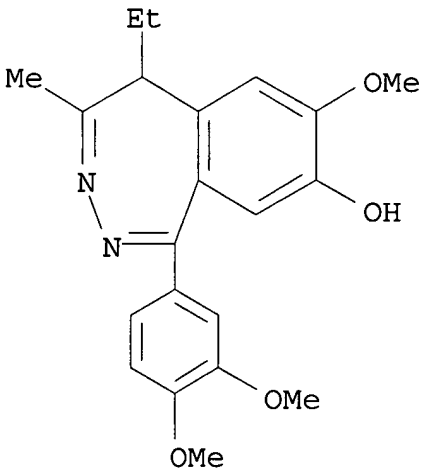
IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-

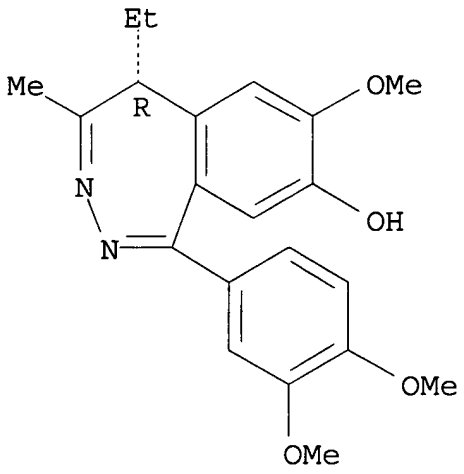
methoxy-8-hydroxy-5H-2,3-benzodiazepine **697754-53-3P**, (R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of optically pure (R)-2,3-benzodiazepines for treatment of LTB4-mediated inflammatory disorders)

RN 95500-09-7 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



RN 697754-53-3 ZCAPLUS
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 9 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:451630 ZCAPLUS
DN 141:23557
ED Entered STN: 04 Jun 2004
TI Preparation of (R)-2,3-benzodiazepines for the treatment of neutropenia.
IN Harris, Herbert W.; Kucharik, Robert F.
PA Vela Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-5513
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 7022700	B2	20060404		
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02

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200312
03

WO 2004050615 A3 20040805
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003302682 A1 20040623 AU 2003-302682

200312
03

PRAI US 2002-309527 A2 20021203
WO 2003-US38634 W 20031203

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004106601	ICM	A61K031-5513
	INCL	514221000
	IPCI	A61K0031-55 [I,A]; A61K0031-553 [I,A]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513; A61K031/5513+M; A61K045/06
US 2004138210	IPCI	A61K0031-5513 [ICM,7]; A61K0031-551 [ICM,7,C*]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	NCL	514/221.000
	ECLA	A61K031/5513; A61K031/5513+M; A61K045/06
WO 2004050615	IPCI	C07D [ICM,7]
	IPCR	A61K0031-551 [I,C*]; A61K0031-5513 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
	ECLA	A61K031/5513; A61K031/5513+M; A61K045/06
AU 2003302682	IPCI	A61K0031-55 [ICM,7]; A61K0031-43 [ICS,7];

A61K0031-429 [ICS,7,C*]; A61K0031-425 [ICS,7];
A61K0031-70 [ICS,7]; A61K0031-41 [ICS,7];
A61K0031-545 [ICS,7]
IPCR A61K0031-551 [I,C*]; A61K0031-5513 [I,A];
A61K0045-00 [I,C*]; A61K0045-06 [I,A]
OS MARPAT 141:23557
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = alkylhydrocarbyl, heteroalkyl; R2 = H, hydrocarbyl, wherein R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; X = (R3)n; R3 = O-alkyl, OH, O-acyl, etc.; n = 1-3; R4, R5 = O-alkyl, OH, O-acyl, etc., wherein R4 and R5 may combine to form a 5-, 6-, 7-membered heterocyclic ring] and their pharmaceutically acceptable salts were prepd. For example, condensation-cyclization of diketone II, e.g., prepd. from 3-methoxy-4-hydroxybenzoic acid in 7-steps, and hydrazine hydrate afforded racemic benzodiazepine III. In a 16-day study of neutrophil prodn. in rats, one example of compd. I, e.g., R-tofisopam, significantly increased neutrophil levels in a dose-dependant manner. Compds. I are claimed useful for increasing the prodn. of neutrophils.

ST benzodiazepine prepn neutropenia neutrophil; tofisopam chiral benzodiazepine prepn neutropenia neutrophil

IT Glycosides
(amino, medicaments with; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Thyroid gland
(medicaments with inhibitors of; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Analgesics
Antibiotics
Antihistamines
Antimalarials
Cardiovascular agents
Chemotherapy
Psychotropics
Rauvolfia

(medicaments with; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Tetracyclines
(medicaments with; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Agranulocytosis
(neutropenia, treatment of; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Anti-inflammatory agents
(nonsteroidal, medicaments with; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Anti-AIDS agents
Antitumor agents
Antiviral agents
Human
Immunostimulants
(prepn. of benzodiazepines for the treatment of neutropenia.)

IT Human immunodeficiency virus 1
Immunodeficiency
Ionizing radiation
Neoplasm
(treatment of neutropenia from; prepn. of benzodiazepines for the treatment of neutropenia.)

IT Infection
(viral, treatment of neutropenia from; prepn. of benzodiazepines for the treatment of neutropenia.)

IT 63-74-1, Sulfonamide
(medicaments with antibiotics of; prepn. of benzodiazepines for the treatment of neutropenia.)

IT 50-33-9, Phenylbutazone, biological studies 50-47-5, Desipramine 50-49-7, Imipramine 50-78-2, Aspirin 51-06-9, Procainamide 51-28-5, Dinitrophenol, biological studies 51-52-5, Propylthiouracil 52-01-7, Spironolactone 52-67-5, Penicillamine 52-86-8, Haloperidol 53-86-1, Indomethacin 54-05-7, CHLOROQUINE 54-85-3, Isoniazid 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-53-4, Meprobamate 58-14-0, Pyrimethamine 58-15-1, Aminopyrine 58-54-8, Ethacrynic acid, 58-94-6, Thiazide 59-66-5, Acetazolamide 59-92-7, Levodopa, biological studies 60-56-0, Methimazole 64-77-7, Tolbutamide 64-86-8, Colchicine 67-20-9, Nitrofurantoin 67-52-7D, 2,4,6(1H,3H,5H)-Pyrimidinetrione, derivs. 68-89-3, Dipyrone 74-55-5, Ethambutol 80-08-0, Dapsone 83-12-5, Phenindione 83-89-6, Quinacrine 86-22-6 86-54-4,

Hydralazine 89-57-6, Mesalazine 91-81-6, Tripelennamine 92-84-2, Phenothiazine 94-20-2, Chlorpropamide 99-66-1, Valproic acid 104-06-3, Thiacetazone 118-42-3, Hydroxychloroquine 123-56-8, Succinimide 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 127-48-0, Trimethadione 130-95-0, Quinine 141-90-2, Thiouracil 298-46-4, Carbamazepine 302-04-5, Thiocyanate, biological studies 302-79-4, Retinoic acid, 303-49-1, Clomipramine 315-30-0, Allopurinol 364-62-5, Metoclopramide 364-98-7, Diazoxide 461-72-3, Hydantoin 493-78-7, Methaphenilene 525-66-6, Propranolol 554-57-4, Methazolamide 555-30-6, Methyldopa 575-54-2, Penicillins 599-79-1, Sulfasalazine 738-70-5, Trimethoprim 1404-55-3, Ristocetin 2022-85-7, Flucytosine 2784-55-6, Thenalidine 3313-26-6, Thiothixene 5786-21-0, Clozapine 7778-74-7, Potassium perchlorate 10540-29-1, Tamoxifen 11111-12-9, Cephalosporins 12794-10-4D, Benzodiazepine, derivs. 13292-46-1, Rifampin 13311-84-7, Flutamide 14028-44-5, Amoxapine 14769-73-4, Levamisole 15687-27-1, Ibuprofen 21679-14-1, Fludarabine 22232-54-8, Carbimazole 22494-42-4, Diflunisal 24219-97-4, Mianserin 26171-23-3, Tolmetin 27790-75-6, Dihydropyridine 30516-87-1, Zidovudine 31431-39-7, Mebendazole 36877-68-6, Nitroimidazole 37640-71-4, Aprindine 38194-50-2, Sulindac 41859-67-0, Bezafibrate 51234-28-7, Benoxaprofen 51481-61-9, Cimetidine 54063-53-5, Propafenone 55142-85-3, Ticlopidine 59277-89-3, Acyclovir 62571-86-2, Captopril 64221-86-9, Imipenem 66357-35-5, Ranitidine 76824-35-6, Famotidine 81840-15-5, Vesnarinone 82009-34-5, Cilastatin 85721-33-1, Ciprofloxacin 91161-71-6, Terbinafine 106266-06-2, Risperidone
(medicaments with; prepn. of benzodiazepines for the treatment of neutropenia.)

IT 75114-20-4P 82059-50-5P **95500-09-7P** 697754-50-0P 697754-51-1P 697754-52-2P **697754-53-3P** 697754-54-4P 697754-55-5P
(prepn. of benzodiazepines for the treatment of neutropenia.)

IT 64-17-5, Ethanol, reactions 75-03-6, Iodoethane 93-07-2, 3,4-Dimethoxybenzoic acid 100-39-0, Benzyl bromide 121-34-6, 3-Methoxy-4-hydroxybenzoic acid 302-01-2, Hydrazine, reactions 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 7803-57-8, Hydrazine hydrate 55300-10-2
(prepn. of benzodiazepines for the treatment of neutropenia.)

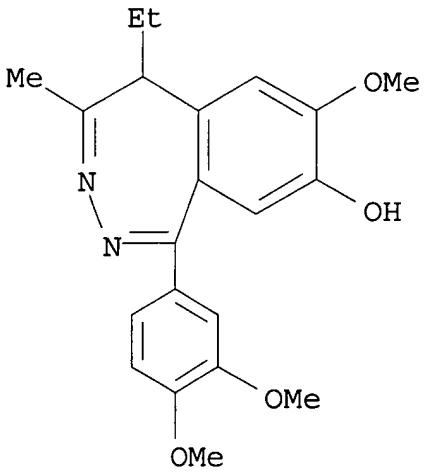
IT 617-05-0P, Ethyl-3-methoxy-4-hydroxybenzoate 6346-05-0P, 4-Methoxy-3-(phenylmethoxy)benzaldehyde 618056-32-9P,

4-((1Z)-1-Ethylprop-1-enyl)-1,2-dimethoxybenzene 618056-34-1P, 3-[4,5-Dimethoxy-2-[[4-methoxy-3-(phenylmethoxy)phenyl]carbonyl]phenyl]pentan-2-one 618056-36-3P, 3-[2-[(3-Hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one 697754-56-6P, 3-(3,4-Dimethoxyphenyl)pentanol 697754-57-7P, 3-[2-[(3,4-Dimethoxyphenyl)carbonyl]-4-hydroxy-5-methoxyphenyl]pentan-2-one
(prepn. of benzodiazepines for the treatment of neutropenia.)

IT **95500-09-7P 697754-53-3P**
(prepn. of benzodiazepines for the treatment of neutropenia.)

RN 95500-09-7 ZCAPLUS

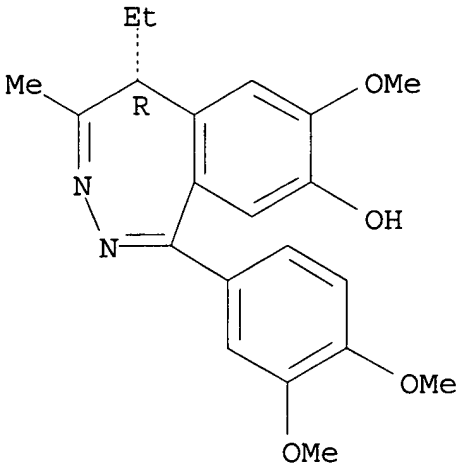
CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



RN 697754-53-3 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 10 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:851280 ZCAPLUS
DN 139:350760
ED Entered STN: 30 Oct 2003
TI Preparation of 2,3-benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia.
IN Harris, Herbert W.; Kucharik, Robert F.
PA Vela Pharmaceuticals, Inc., USA
SO U.S., 18 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-551
INCL 514221000
CC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6638928	B1	20031028	US 2002-309526	20021203
CA 2508546	AA	20040617	CA 2003-2508546	20031203

WO 2004050616 A2 20040617 WO 2003-US38637
200312
03

WO 2004050616 A3 20040910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003297663 A1 20040623 AU 2003-297663
200312
03

EP 1567162 A2 20050831 EP 2003-812516
200312
03
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2006510632 T2 20060330 JP 2004-557604
200312
03

PRAI US 2002-309526 A 20021203
WO 2003-US38637 W 20031203

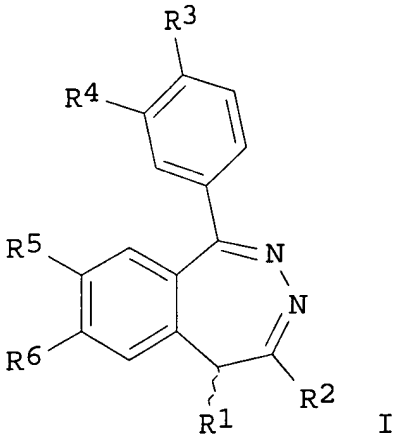
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6638928	ICM	A61K031-551
	INCL	514221000
	IPCI	A61K0031-551 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	NCL	514/221.000
	ECLA	A61K031/551
CA 2508546	IPCI	A61K0031-551 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551

WO 2004050616	IPCI	C07D [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551
AU 2003297663	IPCI	A61K0031-551 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
EP 1567162	IPCI	A61K0031-551 [ICM,7]
	IPCR	A61K0031-551 [I,A]; A61K0031-551 [I,C*]
	ECLA	A61K031/551
JP 2006510632	IPCI	A61K0031-551 [I,A]; C07D0243-02 [I,A]; C07D0243-00 [I,C*]; A61P0001-00 [I,A]; A61P0001-14 [I,A]
	FTERM	4C086/AA01; 4C086/AA02; 4C086/BC53; 4C086/MA01; 4C086/MA04; 4C086/NA14; 4C086/ZA66; 4C086/ZA69

OS MARPAT 139:350760

GI



I

AB Title compds. [I; R1 = hydrocarbyl, heteroalkyl; R2 = H, hydrocarbyl; R1R2 = atoms to form a carbocyclic, heterocyclic 5-6 membered ring; 1 of R3-R6 = OH, and the rest = hydrocarbyl, CF3, hydrocarbyloxy, acyloxy, NH2, alkylamino, dialkylamino, acylamino, halo; R5R6 = atoms to form a 5-7 membered heterocyclic ring], were prepd. Thus, 3-[2-[(3-hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one (prepn. given) and N2H4 were refluxed 0.5 h. in EtOH; the cooled soln. was satd. with HCl gas, concd., basified with concd. aq. NH3, and extd. with CH2Cl2 to give 1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-

benzodiazepine. The latter at 32 mg/kg i.p. gave 42% inhibition in the glass bead test of colonic propulsive motility in mice.

ST benzodiazepine prepn irritable bowel syndrome nonulcer dyspepsia treatment

IT Intestine, disease
(irritable bowel syndrome, treatment; prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT Dyspepsia
(nonulcer dyspepsia treatment; prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT Human
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT 74950-24-6, 1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(Prepn. of 2,3-benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia.)

IT 75114-20-4P, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT 74950-18-8, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine 74950-21-3, 1-(3-Methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine 74950-36-0, 1-(3-Hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT 121-34-6, 3-Methoxy-4-hydroxybenzoic acid 621-59-0, 3-Hydroxy-4-methoxybenzaldehyde 3943-77-9, Ethyl 3,4-dimethoxybenzoate 185033-64-1, Ethyl 3-methoxy-4-benzyloxybenzoate 618056-40-9, 4-(4-Ethyl-6,7-dimethoxy-3-methylisochromanyl)-1-methoxy-2-(phenylmethoxy)benzene 618056-41-0, 4-((1Z)-1-Ethylprop-1-enyl)-1-benzyloxy-2-methoxybenzene 618056-42-1, 4-(4-Ethyl-6-methoxy-7-benzyloxy-3-methylisochromanyl)-1,2-dimethoxybenzene
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

IT 617-05-0P, Ethyl 3-methoxy-4-hydroxybenzoate 6346-05-0P, 4-Methoxy-3-(phenylmethoxy)benzaldehyde 618056-30-7P,

3-(3,4-Dimethoxyphenyl)pentan-3-ol 618056-32-9P,
4-((1Z)-1-Ethylprop-1-enyl)-1,2-dimethoxybenzene 618056-34-1P,
3-[4,5-Dimethoxy-2-[[4-methoxy-3-(phenylmethoxy)phenyl]carbonyl]phenyl]pentan-2-one 618056-36-3P, 3-[2-[(3-Hydroxy-4-methoxyphenyl)carbonyl]-4,5-dimethoxyphenyl]pentan-2-one 618056-37-4P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-3-ol 618056-38-5P, 3-(3-Methoxy-4-benzyloxyphenyl)pentan-2-ol 618056-39-6P, 3-[4-Benzyloxy-5-methoxy-2-[(3,4-dimethoxyphenyl)carbonyl]phenyl]pentan-2-one
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD

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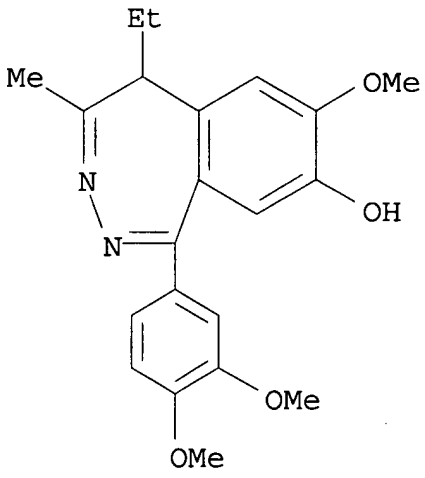
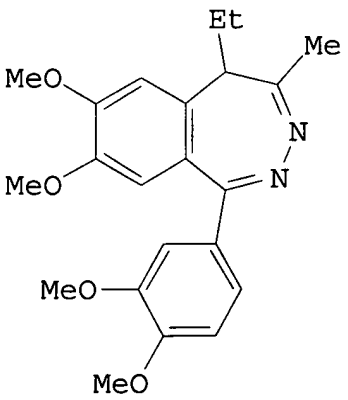
IT **95500-09-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine
(prepn. of benzodiazepines for treatment of irritable bowel syndrome and nonulcer dyspepsia)

RN 95500-09-7 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)



L9 ANSWER 11 OF 11 ZCAPLUS COPYRIGHT 2006 ACS on STN
AN 1985:125037 ZCAPLUS
DN 102:125037
ED Entered STN: 20 Apr 1985
TI Investigation of metabolites of tofizopam in man and animals
AU Tomori, Eva; Elekes, Istvan; Lang, Tibor; Horvath, Gyula
CS Inst. Drug Res., Budapest, H-1325, Hung.
SO Polish Journal of Pharmacology and Pharmacy (1984), 36(4), 423-30
CODEN: PJPPAA; ISSN: 0301-0244
DT Journal
LA English
CC 1-2 (Pharmacology)
GI



I

AB The biotransformation of tofizopam (I) [22345-47-7] was investigated after oral administration in animals and man. Most of the urinary metabolites were conjugated with glucuronic acid. The chief way of the metabolic information of tofizopam is demethylation, however, the demethylation site as well as the rate of the reaction was different in various species.

ST tofizopam metab

IT 74950-18-8 74950-21-3 74950-24-6 74950-36-0 75114-20-4
95500-09-7
(formation of, as tofizopam metabolite in humans and lab. animals)

IT 22345-47-7D, metabolites, glucuronic acid conjugates
(formation of, in humans and lab. animals)

IT 22345-47-7
(metab. of, in humans and lab. animals)

IT **95500-09-7**
(formation of, as tofizopam metabolite in humans and lab. animals)

RN 95500-09-7 ZCAPLUS

CN 5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl- (9CI) (CA INDEX NAME)